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JAK-STAT Inhibitors: A Game Changer, from Rheumatology to Gastroenterology

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ABSTRACT

Autoimmune diseases represent a growing global health concern, with a rising incidence and prevalence across the globe, and are expected to exponentially rise through 2050. This increase is attributed to factors such as urbanization, lifestyle changes, and improved healthcare access. Historically, the management of autoimmune and immune-mediated diseases has revolved around broad immunosuppression, primarily relying on corticosteroids and other disease-modifying agents. These have limitations such as non-specific immunosuppression, increased risk of infection, and end-organ damage. In subsequent years, the therapeutic armamentarium expanded to include biologic agents that selectively target individual pro-inflammatory cytokines, such as tumor necrosis factor (TNF) alpha inhibitors and anti-integrin or anti-interleukin-12/23 therapies. Although biologics have improved disease outcomes and enabled more targeted intervention, their use is constrained by factors such as immunogenicity, the need for parenteral administration, and a persistent risk of adverse effects, including serious infections and malignancy. These limitations have underscored the need for novel therapeutic modalities with improved efficacy, safety, and patient convenience. The advent of Janus kinase (JAK)-signal transducer and activator of transcription (STAT) inhibitors has transformed the therapeutic landscape of immune-mediated diseases. Tofacitinib, upadacitinib, and filgotinib are orally administered small molecules that inhibit intracellular signaling of pro-inflammatory cytokines, which modulate several pathways simultaneously. In recent years, a therapeutic paradigm shift has emerged in the field of gastroenterology, with JAK inhibitors being increasingly utilized for the management of Inflammatory Bowel Disease (IBD). These have demonstrated efficacy in both induction and maintenance of remission, including among patients refractory to anti-TNF and other biologic therapies. This article will focus on the evolving role and paradigm shift in the use of JAK-STAT inhibitors from rheumatology to gastroenterology.

Introduction

The global incidence and burden of immune-mediated diseases, such as rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, systemic lupus erythematosus, Crohn's disease, ulcerative colitis, and psoriasis, are rising, with projections indicating continued growth through 2050.[1] With rising urbanization, improvement in lifestyle, and accessibility to quality healthcare resources, these conditions, once considered to be prevalent in the industrialized world, have shown an increase in prevalence worldwide.[2] Historically, management of autoimmune diseases such as rheumatological and inflammatory bowel diseases (IBD) has relied on suppression of the immune system primarily by corticosteroids. Over the past two decades, conventional immunosuppressants (e.g., methotrexate, azathioprine) and biologic agents targeting individual cytokines (e.g., TNF inhibitors, anti-integrin, anti-IL-12/23 therapies) have been widely used. However, these agents have shown limited efficacy with various limitations such as immunogenicity, parenteral administration, and significant adverse effect profiles, including infection, malignancy, and organ toxicity, etc have restricted their use.[3,4]

The advent of Janus kinase (JAK)-signal transducer and activator of transcription (STAT) inhibitors marked a paradigm shift in the treatment of these disorders.[5] JAK-STAT inhibitors, such as tofacitinib, upadacitinib, and filgotinib, are orally administered small molecules that inhibit intracellular signaling of multiple pro-inflammatory cytokines. Unlike biologics that block individual cytokines, JAK inhibitors can modulate several cytokine pathways simultaneously. Tofacitinib exhibits broader JAK inhibition, while upadacitinib and filgotinib are more selective for JAK1.[6] Their low immunogenicity, oral administration, and rapid onset of action further distinguish them from traditional biologics **(Table1)**.

Initially developed for rheumatological conditions, JAK-STAT inhibitors have revolutionized IBD management and achievement of endoscopic, histological, and clinical remission. This review outlines the paradigm shift in the therapeutic application of JAK-STAT inhibitors—from their initial use in rheumatologic diseases to their emerging role in the treatment of inflammatory bowel disease—by summarizing the current evidence supporting their efficacy in gastroenterological practice.

Mechanism and Pathophysiology

The JAK-STAT signaling pathway involves a membrane-bound cytokine receptor linked to Janus kinases (JAKs), which are intracellular tyrosine kinases, and signal transducers and activators of transcription (STATs). The JAK family includes four members: JAK1, JAK2, JAK3, and TYK2.[7] Upon cytokine binding, JAKs—located on the cytoplasmic portion of the receptor—undergo autophosphorylation and transphosphorylation.[7] This phosphorylation cascade activates STAT proteins, which then dimerize and translocate to the nucleus to initiate transcription of genes involved in inflammation. The pathway is tightly regulated at multiple levels, including by cellular phosphatases that dephosphorylate receptors and STATs to attenuate the signal (Figure 1).

Table 1. Janus kinase (JAK) inhibitors in rheumatologic diseases

Disease/Condition	JAK Inhibitor(s)	Key Trials/Outcomes	Approval Status
Rheumatoid arthritis	Tofacitinib, Baricitinib, Upadacitinib, Filgotinib, Peficitinib	ORAL, RA-BEAM, SELECT series phase III trials showed all JAKi superior to placebo for ACR20/50/70 responses and remission.	All FDA-approved for RA
Psoriatic arthritis	Tofacitinib, Upadacitinib	Phase III trials (OPAL Broaden/Pioneer, SELECT-PsA) showed significant improvement in joint counts, psoriasis, and enthesitis vs placebo. Efficacy was comparable to anti-TNF biologics.	Approved for active PsA
Axial SpA (Ankylosing spondylitis)	Tofacitinib, Upadacitinib, (Filgotinib)	Phase II/III trials demonstrated significant ASAS20 response vs placebo (e.g., SELECT-AXIS, GO-VIBRANT). Upadacitinib showed rapid and sustained ASAS40 responses.	UPA approved for AS and non-radiographic SpA
Systemic lupus erythematosus	Baricitinib	BRAVE trials (Phase III) met primary endpoints (SRI-4 response, arthritis score) with baricitinib vs placebo. Tofacitinib showed promise in small studies.	Not yet approved
Other/Overlap diseases	_	JAK inhibitors are effective in some vasculitides/dermatologic autoimmune diseases.	Expanding (e.g., alopecia areata)

Abbreviations: *RA, rheumatoid arthritis; PsA, psoriatic arthritis; SpA, spondyloarthritis; AS, ankylosing spondylitis; SLE, systemic lupus erythematosus; TNF, tumor necrosis factor; UPA, upadacitinib; ACR, American College of Rheumatology response criteria; ASAS, Assessment of SpondyloArthritis International Society response criteria; SRI, Systemic Lupus Erythematosus Responder Index.*

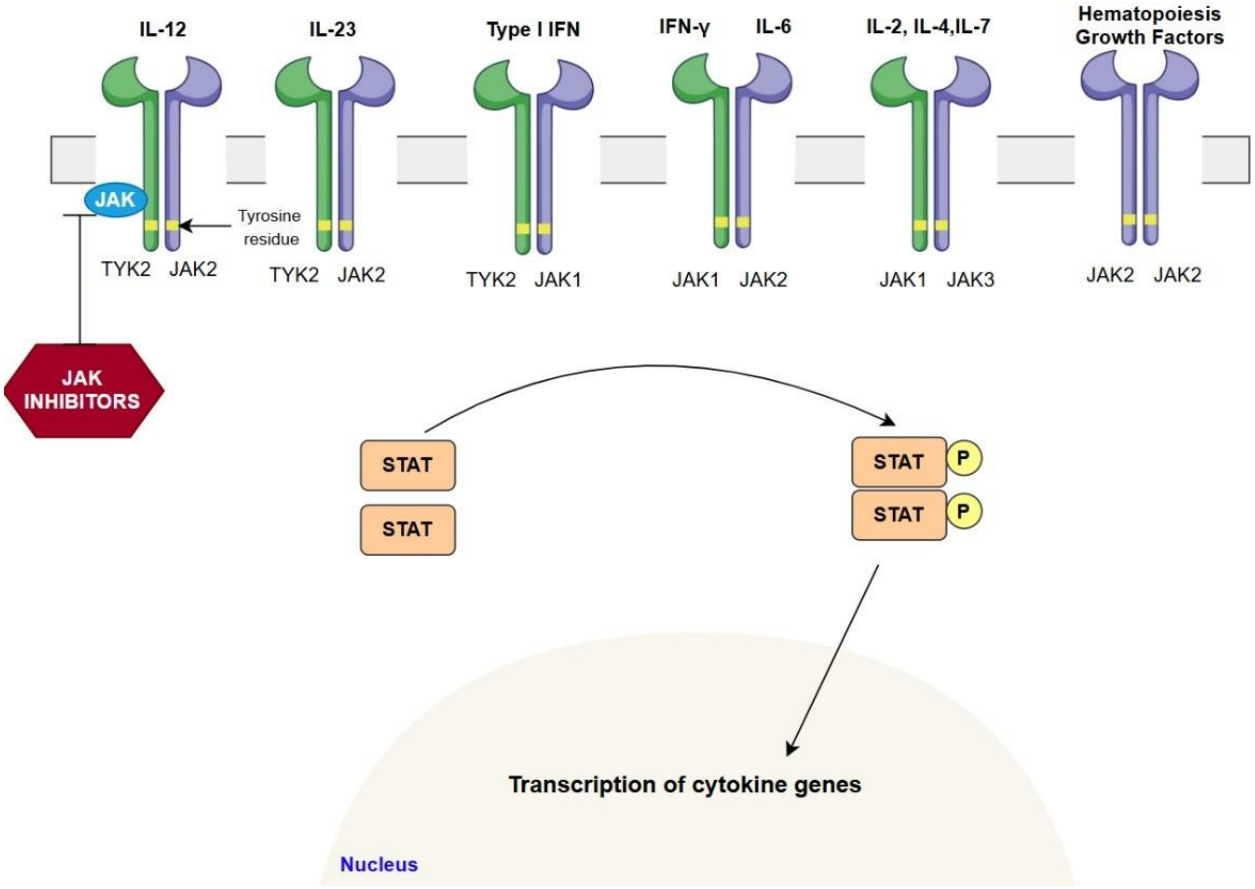

Figure 1. Overview of the JAK-STAT Signaling Pathway and the Mechanism of Action of Janus kinase (JAK) inhibitors

This schematic illustrates the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signaling cascade, a key pathway involved in cytokine receptor signaling. Various cytokines—including IL-12, IL-23, Type I interferons (IFN), IFN-γ, IL-6, IL-2, IL-4, IL-7, and hematopoietic growth factors—bind to their respective membrane-bound receptors, which are associated with specific JAK family members (JAK1, JAK2, JAK3, TYK2). Upon cytokine binding, receptor dimerization occurs, leading to trans-phosphorylation of JAKs and subsequent phosphorylation of receptor-associated tyrosine residues. This facilitates the recruitment and phosphorylation of STAT proteins, which then dimerize and translocate to the nucleus to drive transcription of target cytokine-responsive genes. JAK inhibitors act upstream by blocking the activity of JAK kinases, thereby preventing STAT activation and downstream transcriptional responses, offering a targeted therapeutic approach for inflammatory and autoimmune diseases.

Ulcerative Colitis (UC) and Crohn's Disease (CD), this pathway mediates the effects of pro-inflammatory cytokines such as IL-6, IL-12, IL-23, and IFN-γ, driving chronic mucosal inflammation, epithelial barrier dysfunction, and immune cell recruitment.[8] The IL-6/JAK1/STAT3 axis is particularly important in UC, while the IL-12/IL-23 axis (signaling through JAK2 and TYK2) is more prominent in CD.[9] In rheumatological diseases, JAK-STAT signaling underlies the activation and survival of autoreactive T and B cells, production of inflammatory mediators, and tissue destruction. Genetic studies have identified polymorphisms in JAK and STAT genes that confer susceptibility to IBD and rheumatological diseases.

The selectivity of JAK inhibitors for particular isoforms (JAK1, JAK2, JAK3, TYK2) is a key factor influencing both efficacy and toxicity. First-generation therapeutic drugs, like tofacitinib, inhibit a broader range of JAK isoforms, whereas second-generation drugs such as upadacitinib and filgotinib exhibit more selectivity

for JAK1. This selectivity affects the range of cytokine inhibition and, hence, the pharmacokinetics and pharmacodynamics of each drug.[10]

History and Role of JAK-STAT Inhibitors in Rheumatology

JAK-STAT inhibitors have been recognized as efficacious treatments for rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis. It has been well established through clinical trials and meta-analyses that JAK inhibitors are superior to placebo and are at least non-inferior to tumor necrosis factor inhibitors (TNFi) regarding key clinical endpoints, including ACR20/50/70 responses (Note: The American College of Rheumatology defines ACR20, ACR50, and ACR70 response criteria as at least 20%, 50%, and 70% improvement, respectively).[11–16] A meta-analysis of 39 studies with 16,894 individuals evaluated six JAK inhibitors (tofacitinib, baricitinib, upadacitinib, filgotinib, peficitinib, and decernotinib) and determined that all drugs exhibited superior ACR responses relative to placebo. Decernotinib 300 mg exhibited the most significant ACR50 response, whereas upadacitinib 15 mg presented the greatest likelihood of attaining remission and minimal disease activity in DMARD-naive patients.[11,12] Indirect comparisons indicate that upadacitinib may exhibit statistically superior response rates relative to tofacitinib and baricitinib.[13,17]

Combination therapy with methotrexate (MTX) augments the effectiveness of JAK inhibitors. This yields higher ACR response rates and greater attainment of low disease activity/remission compared to JAK monotherapy.[14,18] Phase 2 and 3 trials have demonstrated the efficacy of tofacitinib, upadacitinib, and filgotinib in PsA and axSpA, with outcomes comparable to biologic DMARDs.[19] Upadacitinib, notably, achieved high ACR20/50/70 responses in the SELECT-PsA trials and has emerged as a preferred oral option for PsA.[20] It is now FDA-approved for active PsA, whereas filgotinib and baricitinib are not indicated for PsA as of 2025. In axial spondyloarthritis, upadacitinib became the first JAK inhibitor approved for ankylosing spondylitis (radiographic axSpA) and non-radiographic axSpA, based on the SELECT-AXIS trials.[21]

Transition to Gastroenterology

Their success in rheumatology, marked- swift onset of action, oral delivery, ability to simultaneously target multiple cytokines, and effectiveness in patients unresponsive to traditional and biologic DMARDs, led to discovery in other immune-mediated pathologies with comparable cytokine patterns.[4,9,22] Pathogenesis of IBD (UC and CD) also shares the JAK-STAT pathway. As a result, JAK inhibitors such as tofacitinib, upadacitinib, and filgotinib were evaluated in clinical trials for IBD, demonstrating significant efficacy in inducing and maintaining remission, especially in patients with moderate-to-severe disease who had failed biologic therapies.[23] This transition from rheumatology to gastroenterology demonstrates a paradigm shift in the treatment of autoimmune chronic inflammatory gastrointestinal indications.

Clinical Trials and Comparative Efficacy in IBD

The success of JAK inhibitors in rheumatology paved the way for research in IBD, where the need for oral, non-immunogenic therapies with rapid onset was unmet.

Ulcerative Colitis: Tofacitinib was the first JAK inhibitor approved for moderate-to-severe UC, based on the pivotal phase III OCTAVE Induction and Maintenance trials (Table 2). By week 8 of induction, ~18% of tofacitinib-treated UC patients achieved remission, compared to ~8% on placebo; at 52 weeks of maintenance, remission was ~34% on tofacitinib versus ~11% on placebo.[24] The TACOS trial was a randomized, double-blind, placebo-controlled study in patients hospitalized with acute severe ulcerative colitis, demonstrating that adding tofacitinib (10 mg three times daily for 7 days) to intravenous corticosteroids significantly improved the day-7 response (83% vs 60% on steroids alone) and reduced the need for rescue therapy or colectomy.[22] Upadacitinib was evaluated in the U-ACHIEVE and U-ACCOMPLISH Phase 3 trials for UC, showing high

rates of clinical and endoscopic remission in both biologic-naïve and biologic-experienced patients. Induction therapy with upadacitinib 45 mg led to clinical remission at 8 weeks in ~26–33% of UC patients (depending on prior biologic exposure), versus ~5–14% with placebo. Endoscopic improvement was also significantly higher (e.g., ~41% on upadacitinib vs ~7% on placebo in one induction study).[25,26] Filgotinib 200 mg induced clinical remission in ~26% of UC patients by week 10 (placebo ~15%) and maintained remission in ~37% at week 54 (placebo ~11%). Notably, Filgotinib's safety profile in UC was favorable, with lower rates of serious infections and herpes zoster compared to tofacitinib, reflecting its JAK1-selectivity. Filgotinib, brand name Jyseleca, received approval for UC in Europe and Japan in late 2021, but it is not approved in the United States due to FDA concerns about the 200 mg dose and male reproductive toxicity.[27]

Table 2: Janus kinase (JAK) inhibitors in Ulcerative Colitis (UC)

JAK Inhibitor	Pivotal Trials (Phase)	Outcomes	Approval Status
Tofacitinib	OCTAVE 1&2 (Phase III induction); OCTAVE Sustain (maintenance)	Induction remission: 18.5% vs 8.2% (OCTAVE1); 16.6% vs 3.6% (OCTAVE2). Maintenance remission (52 wk): 34.3% (5 mg BID) & 40.6% (10 mg BID) vs 11.1%	Approved (FDA 2018) for moderate-severe UC; EMA approved.
Upadacitinib	U-ACHIEVE UC1 & UC2 (Phase III induction); U-ACHIEVE UC3 (maintenance)	Induction remission (wk8): 26–34% on 45 mg QD vs 4–5% on placebo. Maintenance (wk52): 42% (15 mg) & 52% (30 mg) vs 12% on placebo	Approved (FDA 2022, EMA 2023) for refractory moderate-severe UC.
Filgotinib	SELECTION trial (Phase IIb/III: induction wk10, maintenance wk58)	Induction (wk10): remission ~20–30% vs ~10% placebo. Maintenance: higher remission at wk58 with 200 mg	Approved (EMA 2021) for moderate–severe UC refractory to biologics
Peficitinib	Phase IIb (8 wk induction)	Failed to show dose-response trend; no significant induction of remission.	Development halted (no approval).
Others (e.g., TD-1473)	Phase II studies	Early trials did not meet endpoints (izencitinib/TD-1473 failed in a 12-wk dose-ranging study).	Not approved.

Abbreviations: *RA, rheumatoid arthritis; PsA, psoriatic arthritis; SpA, spondyloarthritis; AS, ankylosing spondylitis; SLE, systemic lupus erythematosus; TNF, tumor necrosis factor; UPA, upadacitinib; ACR, American College of Rheumatology response criteria; ASAS, Assessment of SpondyloArthritis International Society response criteria; SRI, Systemic Lupus Erythematosus Responder Index.*

Crohn's Disease: The advancement of JAK inhibitors in Crohn's disease has been complex. Tofacitinib failed to achieve primary endpoints in phase II trials for Crohn's disease, resulting in the cessation of its development for this application.[28,29] Conversely, filgotinib and upadacitinib have exhibited success in phase II and III trials. Upadacitinib, however, achieved positive results in Phase 3 Crohn's studies and is now an approved therapy (in 2023, it became the first oral treatment for moderate-to-severe Crohn's disease in the US, Europe, and other regions). In two induction trials (U-EXCEED and U-EXCEL), upadacitinib 45 mg once daily produced clinical remission by 12 weeks in ~40–49% of Crohn's patients, versus 21–29% on placebo (remission defined by Crohn's Disease Activity Index). Endoscopic response at 12 weeks was achieved in ~45% of upadacitinib-treated patients compared to ~13% on placebo. In the maintenance trial (U-ENDURE), responders were re-randomized to upadacitinib 15 mg or 30 mg daily vs placebo; after 52 weeks, clinical remission was maintained in ~36–47% on upadacitinib (dose-dependent) vs ~15% on placebo.[30–33] Filgotinib, in contrast, showed promise in a Phase 2 Crohn's trial (FITZROY) but did not meet its co-primary endpoints in the Phase 3 DIVERSITY program.[34,35] The two induction cohorts of DIVERSITY failed to demonstrate a significant benefit of filgotinib over placebo at week 10 (no difference in clinical remission or endoscopic response). While the maintenance phase of DIVERSITY indicated filgotinib 200 mg could sustain remission (e.g., 44% on filgotinib vs 26% on placebo at week 58 achieved clinical remission; endoscopic response 30% vs 9%).[35] Thus, Filgotinib's Crohn's development was halted (Table 3).

Table 3: ***Janus kinase (JAK) inhibitors*** in Crohn's Disease (CD)

JAK Inhibitor	Trial (Phase)	Outcomes	Status/Notes
Tofacitinib	Phase II induction and Maintenance	Failed to meet primary endpoint (CDAI remission at wk8); no significant clinical benefit.	Not approved for Crohn's.
Filgotinib	FITZROY (Phase II induction 10 wk)	Remission at wk10: 47% on 200 mg vs 23% on placebo (p=0.0077)	Phase III studies conducted; not approved yet.
Upadacitinib	U-EXCEED & U-EXCEL (induction); U-ENDURE (maintenance)	Week-52 CDAI remission: 37% (15 mg) and 48% (30 mg) vs 15% placebo; superior endoscopic remission	FDA-approved (2023) for moderate–severe Crohn's
Peficitinib	Phase II	Data limited; no signals of efficacy published.	No further development in CD.
Others (TD-1473, etc.)	Early-phase	TD-1473 failed to meet endpoints; other gut-selectives discontinued.	Not approved.

Abbreviations: *CDAI = Crohn's Disease Activity Index; FDA = Food and Drug Administration; JAK = Janus kinase.*

Other GI Disorders: Beyond IBD, the JAK-STAT pathway is implicated in eosinophilic gastrointestinal diseases (EGIDs) such as eosinophilic esophagitis (EoE), gastritis/enteritis, and colitis. These conditions are driven by type-2 cytokines (IL-5, IL-13) that signal via JAK-STAT. To date, no JAK inhibitor is specifically approved for EGIDs, but there are compelling case reports. For example, a patient with long-standing eosinophilic esophagitis, gastritis, and enteritis, with eosinophilia, achieved improvement on tofacitinib 5 mg BID: after 6 months, both endoscopically and clinically. Similarly, in eosinophilic colitis, a small case series (four adults) reported complete clinical and histologic remission using JAK inhibitors: two patients on baricitinib (4 mg QD) and two on upadacitinib (15 mg QD) – all improved within weeks (Table 4).

Table 4: Janus kinase (JAK) inhibitors in Other Gastrointestinal Disorders

Condition	JAK Inhibitor(s)	Outcome
Eosinophilic esophagitis/gastroenteritis	Tofacitinib 5 mg BID	Case of refractory EGIDs(esophagitis, stomach, duodenum): symptoms resolved, endoscopic and histologic eosinophilia normalized after 6 months
Eosinophilic colitis	Upadacitinib 15 mg QD; Baricitinib 4 mg QD	4 patients: rapid improvement; colon biopsies showed remission
Eosinophilic gastritis/duodenitis	Upadacitinib 15 mg QD (+ budesonide)	Case: symptom relief and histologic remission
Other EGIDs	–	No controlled trials; scattered case reports suggest benefit

Abbreviations: *EGIDs = Eosinophilic gastrointestinal disorders; BID = twice daily; QD = once daily.*

Real-World Effectiveness and Patient-Reported Outcomes

Real-world evidence substantiates the efficacy and safety of JAK inhibitors in both gastroenterology and rheumatology, albeit with certain variations.[31,47] Multicenter trials and meta-analyses in IBD indicate that upadacitinib and filgotinib are efficacious in inducing and maintaining remission in both ulcerative colitis and Crohn's disease, even in patients with previous biologic failure. Clinical remission rates for upadacitinib in real-world inflammatory bowel disease cohorts vary between 25% and 55%, with endoscopic remission rates aligning with those seen in randomized controlled trials, but marginally lower due to the more refractory characteristics of real-world populations.[31,47] The oral administration, rapid onset of action, and lack of immunogenicity are valued in both fields, but may be particularly advantageous in IBD, where rapid symptom control and avoidance of parenteral therapies are often desired.[3,22]

Safety Outcomes and Comparative Risks

The concerns for the safety profile of JAK inhibitors persist. JAK inhibitors are linked to an increased incidence of infections (particularly herpes zoster), venous thromboembolism (VTE), and, in some groups, major adverse cardiovascular events (MACE) and malignancies.[48–51] The ORAL Surveillance study in rheumatoid arthritis indicated that tofacitinib was statistically inferior to TNFi regarding the incidence

of major adverse cardiovascular events and malignancies in patients over 50 years old with at least one cardiovascular risk factor.[52,53] Observational studies and meta-analyses demonstrate an elevated risk of herpes zoster and a moderately heightened risk of malignancy in patients treated with JAK inhibitors compared to TNFi, with the absolute risk being most significant in older adults and individuals with additional risk factors.[53,54]

In IBD, the risk profile is more favorable. Risk of severe infection and malignancy is not markedly elevated in comparison to TNFi, and the incidence of MACE is low, potentially attributable to the younger demographic and reduced comorbidity burden of IBD patients.[50,55] The American Gastroenterological Association (AGA) guideline indicates that JAK inhibitors may present an elevated cancer risk compared to TNFi in older persons with cardiovascular risk factors, and advises cautious use in patients with a history of cancer.[56] The risk of herpes zoster is elevated with JAK inhibitors in inflammatory bowel disease; however, the absolute incidence remains lower than in rheumatoid arthritis.

Regulatory Evolution and Therapeutic Positioning

The regulatory status and approved indications of JAK-STAT inhibitors are evolving due to the accumulation of clinical trial data and post-marketing safety signals. In rheumatology, JAK inhibitors are generally approved for use after failure of, or intolerance to, conventional synthetic DMARDs, and may be used before or after biologic agents, depending on regional guidelines and payer policies.[57] The safety concerns identified in the rheumatology population, particularly the increased risk of MACE and malignancy in older adults with cardiovascular risk factors, have led to boxed warnings.[53,56]

The FDA label for JAK inhibitors in ulcerative colitis stipulates their usage exclusively for patients who have previously failed or exhibited sensitivity to TNF antagonists, so designating them as second-line or subsequent therapy. The AGA guideline emphasizes individualized decision-making, taking into account patient preferences, comorbidities, and risk factors for adverse events.[56] In Europe, the European Medicines Agency allows for cautious first-line use in certain high-risk patients but generally mirrors the US approach in restricting use to those who have failed other advanced therapies.[5]

Mechanistic Insights and Next-Generation Agents

Next-generation JAK-STAT inhibitors, especially those aimed at TYK2 and gut-selective drugs, are being developed to overcome the safety and effectiveness constraints of previous JAK inhibitors. TYK2 inhibitors, including deucravacitinib, have significant selectivity and an acceptable safety profile, with early-phase trials indicating efficacy in psoriasis and encouraging outcomes in inflammatory bowel disease and rheumatologic disorders. Dual JAK1/TYK2 inhibitors and gut-selective drugs aim to optimize efficacy while reducing systemic exposure and off-target effects.[25,58,59] These advancements are expected to boost therapy alternatives for IBD and rheumatology.

Limitations and Uncertainties in Current Evidence

Despite the robust evidence base, significant limitations and uncertainties remain, particularly regarding optimal sequencing of therapies and patient selection. Most pivotal trials have relatively short follow-up and highly selected populations, limiting generalizability to real-world practice. There is a paucity of direct head-to-head trials comparing different JAK-STAT inhibitors or comparing JAK inhibitors to other advanced therapies in either IBD or rheumatology. The lack of proven predictive biomarkers that guide patient selection hinders clinical decision-making. The long-term safety profile is not completely determined, particularly for the newer, more selective JAK1 and TYK2 inhibitors.

Conclusion

JAK-STAT inhibitors have transformed the treatment of immune-mediated inflammatory disorders, resulting in a significant shift in clinical and scientific emphasis from rheumatology to gastroenterology. The robust effectiveness of JAK inhibitors in both rheumatoid arthritis and gastroenterology, especially IBD, particularly UC, is supported by comprehensive clinical trial and real-world evidence. The safety profile, although generally acceptable, requires meticulous patient selection and risk stratification, particularly in elderly individuals and those with cardiovascular risk factors. The regulatory environment demonstrates these apprehensions, exhibiting more stringent indications in IBD than in rheumatology. Next-generation medicines, such as TYK2 and gut-selective inhibitors, promise to enhance the benefit-risk balance and broaden therapy options. Further prospective research, long-term surveillance, and personalized, patient-centered care will be essential to fully realize the potential of JAK-STAT inhibitors in both rheumatology and gastroenterology.

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